Multidrug resistance and its reversal.

Volm M.

Department of Oncological Diagnostics and Therapy, German Cancer Research Center, Heidelberg, Germany.

Cross-resistance between different cytostatic agents which are structurally and functionally dissimilar is a common phenomenon called multidrug resistance (MDR). The best characterized mechanism of MDR involves P-glycoprotein. However, this does not completely explain MDR. Within the last few years, two new genes that can confer MDR have been identified (MRP and LRP). Furthermore, topoisomerase II has been associated with a special form of MDR. During the past several years, considerable interest has been shown in strategies to reverse MDR by using pharmacological compounds, monoclonal antibodies, immunotoxins, bispecific antibodies, antisense oligodeoxynucleotides, ribozymes, and albumin-conjugated drugs in in vitro and in vivo assays. All these experimental assays demonstrated that MDR can be circumvented. Two agents that have received the most attention in the clinic are verapamil and cyclosporin A. Despite some promising results (especially in hematological malignancies), the results obtained in the treatment of solid tumors with modulators have so far been quite disappointing. This may be explained by the fact that the MDR phenotype alone does not completely account for the resistance of human cancer. Several other resistance-related proteins (e.g., glutathione S-transferase, metallothionein, O6-alkylguanine-DNA-alkyltransferase, thymidylate synthase, dihydrofolate reductase, heat shock proteins) can be also expressed in resistant tumors. Additionally, cell proliferation, vascularization and apoptosis are involved in resistance.

Publication Types:
- Review
- Review, tutorial

PMID: 9713485 [PubMed - indexed for MEDLINE]

Reversal of multidrug resistance of tumor cells.

Szabo D, Keyzer H, Kaiser HE, Molnar J.

Department of Medical Microbiology, University of Szeged, Szeged, Hungary.

Drug resistance to chemotherapy is rapidly emerging. Resistance to one drug carries over resistance to unrelated anticancer drugs leading to multidrug resistance (MDR). A major factor of MDR is P-glycoprotein (P-gp) mediated ABC transport found in many eukaryotic cells. P-gp acts as a drug eMux pump. The mdr1 gene involved in P-gp 170 protein production is localized in the human chromosome 7 band p2 1.0-21.1. Point mutations after cross-resistance patterns. A variety of stimuli increase the expression of the mdr1 gene: lowered extracellular pH, heat shock, arsenite, cytotoxic agents, anticancer drugs, transfection with oncogenes, HIV-I, and UV-irradiation. An alternative hypothesis to the efflux pump claims that P-gp modifies the intracellular environment to reduce accumulation of anticancer drugs in cancer cells by creating ionic or proton gradients. Chemosensitizers that block P-gp drug extrusion are generally lipid-soluble at physiological pH, possess a basic nitrogen atom and at least two co-planar rings. P-gp blocking does not depend on drug chirality. This opens the way of treating P-gp related MDR with chiral versions of drugs relatively harmless in terms of side-effects. We believe that resistance modifiers combined with cytostatics will chemotherapeutically be more effective for cancer patients.

Publication Types:
- Review
- Review, tutorial

PMID: 11205256 [PubMed - indexed for MEDLINE]

Multidrug resistance (MDR) in cancer. Mechanisms, reversal using modulators of MDR and the role of MDR modulators in influencing the pharmacokinetics of anticancer drugs.

Krishna R, Mayer LD.

Department of Advanced Therapeutics, British Columbia Cancer Agency, BC V5Z 4E6, Vancouver, Canada. rajesh.krishna@bms.com

In recent years, there has been an increased understanding of P-glycoprotein (P-GP)-mediated pharmacokinetic interactions. In addition, its role in modifying the bioavailability of orally administered drugs via induction or inhibition has been also been demonstrated in various studies. This overview presents a background on some of the commonly documented mechanisms of multidrug resistance (MDR), reversal using modulators of MDR, followed by a discussion on the functional aspects of P-GP in the context of the pharmacokinetic interactions when multiple agents are coadministered. While adverse pharmacokinetic interactions have been documented with first and second generation MDR modulators, certain newer agents of the third generation class of compounds have been less susceptible in eliciting pharmacokinetic interactions. Although the review focuses on P-GP and the pharmacology of MDR reversal using MDR modulators, relevance of these drug transport proteins in the context of pharmacokinetic implications (drug absorption, distribution, clearance, and interactions) will also be discussed.

Publication Types:
- Review
- Review literature

PMID: 11033070 [PubMed - indexed for MEDLINE]